REMARKS

In a non-final Office Action dated February 10, 2006 the Examiner in charge of this case rejected the claims of this application. Claims 1, 4, 5 and 7-11 are currently pending in the application; Claims 4, 7 and 9-10 remain withdrawn from consideration as being directed to a non-elected invention; Claims 1, 5, 8 and 11, now under consideration, are rejected under 35 U.S.C. §112, 1st ¶. Applicants respond by submitting the amendments and comments set forth hereinbelow. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

Election/Restrictions

Although applicants continue to traverse the Examiner's requirement for restriction, the finality of the requirement is acknowledged. Accordingly, applicants reserve the right to file a divisional application drawn to non-elected Claims 4, 7 and 9-10.

Claim Amendments

Claims 1 and 11 are amended to reflect multiple "steps" rather than one step. Also, the language "any of the genes" is deleted from Claims 1 and 11 to clarify that any one gene selected from the Markush group, exhibiting a decrease in expression relative to a non-diabetic individual, can be used for diagnosing susceptibility to diabetes. Amended Claim 1 also includes a separate step whereby the expression pattern of the test individual is compared with that of a non-diabetic individual prior to making the diabetes susceptibility diagnosis.

Claim 5 is amended at the Examiner's request to replace the term "considering" with "diagnosing." Also, the last step of Claim 5 is amended to clarify that each gene selected from the Markush group is capable of predicting a susceptibility to diabetes. Amended Claim 8 includes the term "determining" to clarify the second step of the method and to include an antecedent basis for "decreased level of expression." Claim 11 is further amended to include a comparing and diagnosing step relating to the preamble of the claim. Support of these amendments is found throughout the specification, for example, at Table 1, 2 and 3. No new matter is added.

Newly added Claim 12 is included in response to Examiner's remarks at page 3, last ¶ , indicating that applicants' disclosure provides evidence that SREBP, cytochrome c oxidase subunit VII, and stearoyl-CoA desaturase each exhibit decreased expression in adipose tissue of obese mice and that a skilled person would find that useful in diagnosing obesity.

Claim Rejections - 35 USC §112

Claims 1, 5, 8 and 11 are rejected under 35 U.S.C. 112, 1st ¶ for allegedly lacking enablement. Specifically, the Examiner asserts the specification does not include the genes encoding add1/SREBP, cytochrome c oxidase subunit VIIa, and stearoyl-CoA desaturase in adipose tissue as being associated with hyperglycemia and diabetic disease. The Examiner further asserts that "lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention." (see pg. 4 of the Office Action). This rejection is respectfully traversed.

Applicants were the first to discover that a decrease in expression levels of SREBP, cytochrome c oxidase subunit Vlla, and stearoyl-CoA desaturase is associated with diabetes or diabetes susceptibility, as well as obesity and the transition from obesity to diabetes. This association was described by applicants in the present application. Based on this unprecedented discovery it is believed that applicants fairly deserve to obtain broad claim coverage.

Applicants submit that since applicants' filing date researchers in the field have confirmed through numerous reports that diabetes or diabetes susceptibility are associated with (decreased) expression levels of SREBP, cytochrome c oxidase subunit Vlla, and/or stearoyl-CoA desaturase. Applicants submit that these reports along with the fact that it is well known that insulin resistance is related to diabetes or progression to diabetes, establish a relationship between decreased expression of a gene (i.e., SREBP, cytochrome c oxidase subunit Vlla, and/or stearoyl-CoA desaturase) in obese individuals and the levels of expression of those same genes in diabetic individuals. Thus, the enablement was satisfied in the application as filed.

For example, Sewter et al. reports that transcript levels of SREBP1c, the most abundant isoform in adipose tissue, were significantly decreased in the subcutaneous adipose tissue of obese normoglycemic and type 2 diabetic subjects compared with that of non-obese

normoglycemic control subjects. It is well known that rat adipocyte determination differentiation factor 1 gene (add1) is homologous to the human SREBP1c isoform. SREBP1c/add1 is predominantly expressed in adipose tissue. (See Human Obesity and Type 2 Diabetes Are Associated With Alterations in SREBP1 Isoform Expression That Are Reproduced *Ex Vivo* by Tumor Necrosis Factor- *Diabetes* 51:1035-1041 (2002)).

Specifically, to establish the effect of insulin on human SREBP1 gene expression, Sewter et al. explored whether common insulin-resistant states such as obesity and type 2 diabetes were associated with impaired expression of SREBP1. Their data show that both obese normoglycemic and obese type 2 diabetic patients have decreased expression of SREBP1 mRNA in subcutaneous adipose tissue. Using a PCR-based method, they showed that SREBP1c is the most abundant isoform in subcutaneous human adipocytes and that this isoform is markedly reduced in isolated adipocytes from obese patients. These data support the notion that in states of insulin resistance or deficiency, there is a specific decrease in the expression of SREBP1c, suggesting a specific role of this isoform in the mediation of the effect of insulin on lipid metabolism. These data affirm applicants' results that there is an association between decreased expression levels of SREBP and diabetes.

Using another approach, Yang et al. recently attempted to elucidate the roles of adipose tissue in the early development of insulin resistance. In this regard, applicants note that it is well accepted that insulin resistance is the main metabolic feature of type 2 diabetes and several studies indicate that it generally precedes the onset of the disease (see Yki-Järvinen H: Role of insulin resistance in the pathogenesis of NIDDM. *Diabetologia* 38:1378–1388 (1995)).

Yang et al. characterized gene expression profiles of isolated adipose cells of non-diabetic insulin-resistant first-degree relatives of type 2 diabetic patients using oligonucleotide microarrays. Yang et al. disclosed that about 600 genes and expressed sequence tags were differentially expressed in the adipose cells. To verify the microarray findings, expression of genes participating in adipogenesis was studied. In part, the expression of adipogenic transcription factors, such as SREBP-1, was reduced in the adipose tissue. The findings suggest that insulin resistance (a diabetes precursor) is associated with impaired adipogenesis. (See *Biochem Biophys Res Commun.* May 14;317(4):1045-51

(2004)). Thus, furthering applicants' position that a reasonable association exists between decreased expression levels of SREBP and diabetes.

Ducluzeau et al. also demonstrates an association between expression levels of SREBP, diabetes or diabetes susceptibility, as well as obesity and the transition from obesity to diabetes. Ducluzeau et al. characterized the concerted regulation by insulin of expression of 10 genes, including SREBP-1c, related to insulin action in subcutaneous adipose tissue. To verify whether an impaired regulation of the expression of some of these genes is specific or secondary to the metabolic state of type 2 diabetes, age-matched control subjects, type 2 diabetic patients, and insulin-resistant nondiabetic obese subjects were investigated in parallel. A total of 44 subjects were involved in the study. The authors found that in adipose tissue, the mRNA expression of SREBP-1c was significantly reduced both in the non-diabetic obese subjects and the type 2 diabetic patients, as first established by applicants in the present application. (See Regulation by Insulin of Gene Expression in Human Skeletal Muscle and Adipose Tissue Evidence for Specific Defects in Type 2 Diabetes; *Diabetes* 50:1134-1142 (2001)).

Choo et al. also shows an association between expression levels of cytochrome c oxidase (a mitochondrial enzyme) and diabetes or diabetes susceptibility, as well as obesity and the transition from obesity to diabetes. Choo et al. assessed the cellular levels of mitochondrial proteins, cellular mitochondrial DNA content, and mitochondrial function and morphology with MitoTracker staining and electron microscopy, in white adipose tissue of 12-week-old male wild-type, obese (ob/ob), and diabetic (db/db) mice.

Choo et al. demonstrated that levels of mitochondrial proteins were greatly decreased in the adipocytes of db/db mice, but not in those of the wild-type and ob/ob mice. Levels of mitochondrial DNA were also found to be considerably reduced in the adipocytes of db/db mice. MitoTracker staining and electron microscopy revealed that the number of mitochondria was reduced in adipocytes of db/db mice. Respiration and fatty acid oxidation studies indicated mitochondrial dysfunction in adipocytes of db/db mice. Figure 6 shows a decrease in ubiquinone cytochrome c oxidoreductase in the diabetic mice and a restoration of expression after treatment with rosiglitazone (an agent that enhances insulin sensitivity). Thus, Choo et al. establishes a correlation between mitochondrial loss in adipose tissue and

the development of type 2 diabetes. The data presented by Choo et al. also indicate that cytochrome c oxidase is a good marker for testing efficacy of drug treatment in diabetics exhibiting decreased expression of cytochrome c oxidase. (See Mitochondria are impaired in the adipocytes of type 2 diabetic mice, *Diabetologia*, Vol. 49 (4) Pages: 784 - 791 (2006)).

Applicants also submit that an association exists between expression levels of stearoyl-CoA desaturase (SCD) and diabetes or diabetes susceptibility, as well as obesity and the transition from obesity to diabetes. For example, Shimomura et al. established that the expression of SCD is controlled by and directly correlates with the expression of SREBP, known to be associated with diabetes. Since Shimomura et al. places the expression of SCD under SREBP control and applicants have shown above that SREBP expression levels are associated with diabetes, then it logically follows that SCD is associated with diabetes. Thus, a skilled artisan can soundly predict that the expression of SCD is associated with diabetes.

Support for this link between SCD and SREBP expression is found, for instance, in Shimomura et al. (See Nuclear Sterol Regulatory Element-binding Proteins Activate Genes Responsible for the Entire Program of Unsaturated Fatty Acid Biosynthesis in Transgenic Mouse Liver, *J Biol Chem,* 273(52), 35299-35306 (1998)). Shimomura et al. found that overexpressing two of the SREBPs (1a and 2) led to elevated mRNAs for stearoyl-CoA desaturase 1 (SCD1) and stearoyl-CoA desaturase 2 (SCD2). The over expression of SREBPs led to an increase in total SCD activity in liver microsomes. Together, all of these changes would be expected to lead to a marked increase in the concentration of monounsaturated fatty acids in the transgenic livers. Thus, although, Shimomura et al. directly links SCD expression with SREBP expression. In passing, it is also noted that Shimomura et al. does not teach or suggest the association between SREBP or SCD with diabetes or obesity; applicants disclose this association in the present application.

Applicants submit the documents discussed above are disclosed in a Supplemental Information Disclosure Statement submitted herewith.

Next, Claims 1, 5, 8 and 11 are rejected under 35 U.S.C. 112, 2nd ¶ for allegedly being indefinite. Specifically, the Examiner asserts that Claims 1, 5, and 11 are indefinite because it is unclear whether the claims require determining the expression pattern of "any or all "of the genes in the Markush group for diagnosing susceptibility to diabetes. The

Examiner also asserts that the term "considering" is vague and indefinite in Claim 5, since the claim is drawn to a method "for the diagnosis of predisposition to diabetes." Claim 8 is deemed indefinite by the Examiner for lacking an antecedent basis when reciting the limitation " decreased level of expression". Claim 11 is deemed indefinite because it is not clear how determining a "decrease in expression...associated with the transition from obese to diabetic" relates to the preamble of the claim, which recites a method "for the diagnosis or prognosis of obesity, incipient obesity.

In response, applicants amend Claims 1, 5, 8 and 11 as indicated above to clarify the requested language. No new matter is added.

Also, as requested by the Examiner, applicants submit herewith an Associate Power of Attorney.

Accordingly, applicants respectfully request that in view of these claim amendments and comments, the rejection be reconsidered and withdrawn, and that a timely Notice of Allowance be issued in this case.

A petition for extension of time accompanies this response so the response will be deemed to have been timely filed. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055.

Respectfully submitted,

Sara D. Vinarov
Reg. No.: 48,524
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701

TEL 608/251-5000
FAX 608/251-9166